17 September 2020
EMA/500437/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sprycel

dasatinib

Procedure no: EMEA/H/C/000709/P46/047

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 9 June 2020 the MAH submitted completed paediatric study for Sprycel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The submission provided the Addendum 02 to the final Clinical Study Report for study CA180018, Phase 1 Study of SRC, ABL Tyrosine Kinase Inhibitor Dasatinib (BMS-354825) in Children and Adolescents with Relapsed or Refractory Leukemia as requested on 14-Nov-2019.

The final CSR for study CA180018 was submitted to the EMA in November 2011 in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended and was considered fulfilled by CHMP on 16-Feb-2012 (procedure P46 - Pediatric Article 46 Follow-up Measure 035). The final CSR provided preliminary growth and development data as of 28-Jun-2011 database lock (DBL). The **Addendum 01** was submitted in March 2017 (EMEA/H/C/000709/X/0056/G) and provided an update on 7 subjects who had been on study treatment at the time of the final CSR cutoff, and updated safety and efficacy data, up to DBL of 04-Nov-2016.

The purpose of this Addendum 02 is to report the entirety of the growth and development data, and overall survival (OS) results in Philadelphia Chromosome Positive Chronic Myeloid Leukemia in chronic phase (Ph+CP-CML) paediatric patients, which were collected during the study, including the 5-year follow-up period in accordance with the dasatinib agreed PIP (ref. EMEA-000567-PIP01-09-M05) and as reflected in the current RMP v16.1 as 'Routine Pharmacovigilance Activities beyond adverse event reporting and signal detection'.

The paediatric studies included in the 'Long-term safety assessments for clinical evaluation of disorder of growth and development and of bone mineral metabolism' are CA180018, CA180204, CA180226, and CA180372. *To note, a PAM P46 application was submitted to EMA on 27-May-2020 for study CA180204.*

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CA 180018 is a stand-alone study

2.2. Information on the pharmaceutical formulation used in the study

Filmcoated tablets

2.3. Clinical aspects

2.3.1. Introduction

Study CA180018 was one of the first BMS studies that evaluated dasatinib in a pediatric population. The findings helped establish the dose in subsequent studies, and the efficacy results supported the registrational pediatric Study CA180226 leading to approval of dasatinib in newly diagnosed pediatric Ph+ CP-CML patients who are resistant or intolerant to prior therapy including imatinib (Procedure EMEA/H/C/000709/X/0056/G).

CA180018 was a Phase 1, open-label, dose-escalation study in which eligible children and adolescents (≥ 1 to < 21 years of age) with relapsed or refractory leukemia were treated with dasatinib orally once daily. Mandatory LTGD and bone metabolism testing were added to the study that were to be performed annually while subjects were on dasatinib study therapy and for up to 5 years of follow-up after the last dose of study drug. Given that the primary and secondary objectives of Study CA180018 have been achieved, and a final CSR and addendum (Addendum 01) reporting those results have been submitted, the Article 46 obligations for this study have been fulfilled. The present submission of Addendum 02 is considered as an update to provide long-term follow up data to CA180018.

No update to the SPRYCEL Product Information and no update to the Risk Management Plan (RMP) are indicated based on the results of the 5-year follow-up on long-term growth and development in pediatric subjects.

2.3.2. Clinical study

Clinical study number and title; Study CA180018

Methods

Study CA180018 was a Phase 1, open-label, dose-escalation (3+3 design, intra-subject dose scalation) study in which eligible children and adolescents (≥ 1 to < 21 years of age) with relapsed or refractory leukemia were treated with dasatinib orally once daily (QD) until disease progression, intolerable toxicity, or patient/physician preference.

A total of 58 subjects received study treatment. Subjects were grouped into strata based on disease

phase:

- 17 subjects in Stratum 1: Ph+ CP-CML
- 17 subjects in Stratum 2/3: Ph+ CML in accelerated phase (AP), Ph+ CML in myeloid or lymphoid blast phase (BP), Ph+ acute lymphoblastic leukemia (ALL), or Ph+ AML
- 24 subjects in Stratum 4: Ph- ALL or AML

The starting dose level for all strata was 60 mg/m2 QD. Each stratum was escalated independently, following a standard 3+3 dose escalation scheme. Intra-subject dose escalation was allowed based on tolerance and on individual response. Subjects could receive dasatinib QD for up to 2 years, in the absence of disease progression, unacceptable toxicity, or per patient/physician preference. With site-specific Amendments 08 and 09, study therapy could be extended for a further 8 years if clinical benefit persisted after 2 years. Subjects were followed until death or up to 5 years after end of treatment.

Per protocol Amendments 05, 06 and 07, mandatory assessments to monitor LTGD and bone metabolism were to be performed annually while subjects were on study therapy, and then followed up yearly for up to 5 years after the last dose. LTGD data is therefore limited and available only for the 8 subjects who were on treatment and 10 subjects who were in follow-up at the time the amendment was implemented.

Results

All primary and secondary objectives for Study CA180018 were met and previously reported. The final CSR (dated 04-Nov-2011) was submitted in November 2011 to the EMA in accordance with (procedure P46 - Pediatric Article 46 Follow-up Measure 035), which was considered fulfilled (no

further action required) by CHMP on 16-Feb-2012. The final CA180018 CSR provided preliminary growth and development data as of 28-Jun-2011 database lock (DBL).

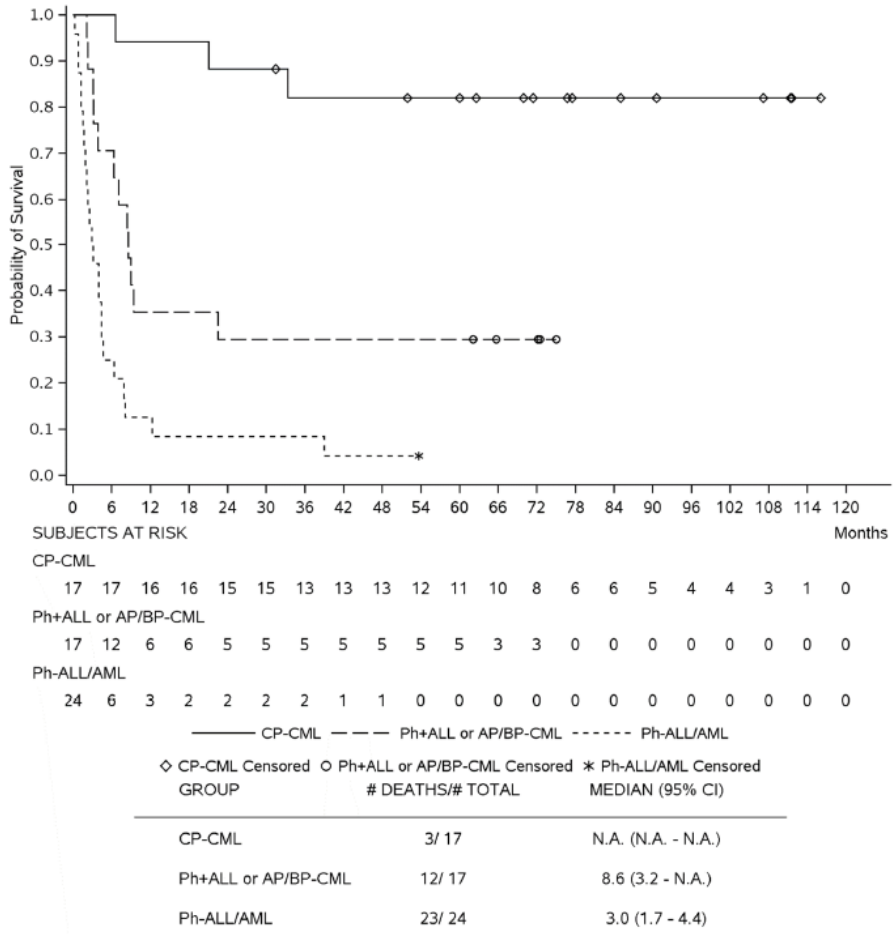
Addendum 01 (dated 01-Mar-2017) was submitted in March 2017 to the EMA within the grouped Extension Application / Type II variation procedure EMEA/H/C/000709/X/0056/G . This CSR provided an update on 7 subjects who had been on study treatment at the time of the final CSR cutoff, and updated safety and efficacy data, up to DBL of 04-Nov-2016.

Data collection is now completed for CA180018 and an addendum (Addendum 02) was prepared in May 2020. The DBL was 19-Apr-2017 and LPLV for Addendum 02 was 01-Sep-2016. The actual last visit date was 22-May-2019. After the DBL, BMS received paper case report forms from 2 additional safety follow-up visits for 1 subject that could not be added to the database and thus was not included in Addendum 02. The subject reported normal physical exam and lab results, and no adverse events or changes to therapy at these follow-up visits. This missing data does not impact the results.

Efficacy results

Addendum 02 to the CSR included final survival data.2 Median OS remained unchanged since the previous addendum (Addendum 01). In CP-CML (Stratum 1), 3 out of 17 subjects (17.6%) died and the median survival for this group had not been reached. In Ph+ ALL or AP/BP-CML (Stratum 2/3), 12 out of 17 subjects (70.6%) died and the median survival for this group was 8.6 months (95% CI: 3.2, N.A.). In Ph- ALL/AML (Stratum 4), 23 out of 24 subjects (95.8%) died and the median survival for this group was 3.0 months (95% CI: 1.7, 4.4). The Kaplan-Meier OS curves are shown in Figure 4.1-1.

Figure 4.1-1: Kaplan Meier Overall Survival - All Treated Subjects



GROUP	# DEATHS/# TOTAL	MEDIAN (95% CI)
CP-CML	3/ 17	N.A. (N.A. - N.A.)
Ph+ALL or AP/BP-CML	12/ 17	8.6 (3.2 - N.A.)
Ph-ALL/AML	23/ 24	3.0 (1.7 - 4.4)

Source: Figure S.5.1 of Addendum 02 to the Final CSR.[2]

Safety results

In Study CA180018, a total of 58 subjects received dasatinib (17 subjects in Stratum 1, 17 subjects in Stratum 2/3, 24 subjects in Stratum 4). Dasatinib was tolerated at doses up to 120 mg/m2 and the doses of 60 and 80 mg/m2 QD were confirmed as the recommended Phase 2 dose for CP-CML and Ph+ALL or AP/BP-CML respectively. Please refer to the previous assessment of details.

Growth and Development Assessments

Tests to monitor LTGD and bone metabolism were added to the study as mandatory protocol procedures (Table 5.1-1). The assessments were to be performed yearly up to 5 years posttreatment. However, at the time these tests were added, only 8 subjects (7, 1, and 0 subjects in Stratum 1, 2/3, and 4, respectively) were on treatment and 10 subjects (6, 4, and 0 in Stratum 1,2/3, and 4, respectively) were in follow-up. Therefore, with the exception of baseline height and weight, which were already collected for all subjects, and body mass index (BMI), which is derived from height and weight, data on other LTGD assessments were limited to the subset of subjects who remained on study or were evaluated in follow-up at the time the changes were implemented.

The Final CSR presented partial LTGD data, but due to the limited follow-up, no definitive conclusions could be made on the effect of dasatinib therapy on growth in pediatric subjects. Data on LTGD and bone metabolism continued to be collected up to 22-May-2019 (LPLV). The cumulative LTGD results are reported here.

Table 5.1-1: List of Long-term Assessments

Height, Weight and BMI	Bone age
Pubertal status (Tanner Stage)	Free T4, TSH
IGF-1, IGF beta-3	FSH, LH in children from 8 years of age
Bone densitometry	Electrolytes (sodium, potassium, magnesium, calcium, chloride, phosphorus)
Urinary N telopeptide	Bone Alkaline Phosphatase

Abbreviations: BMI - body mass index, FSH - follicle stimulating hormone, IGF - insulin-like growth factor, IGF - beta-3 - insulin-like growth factor binding protein-3, LH - luteinizing hormone, TSH - thyroid stimulating hormone

Source: Final CA180018 CSR Table 9.10A

Height, Weight and BMI

Changes from baseline in height, weight, and BMI were described using SI units, z-scores, and percentile shift frequency. Height and weight z-scores are designed to take into account the amount of change that would be expected due to normal growth in children and adolescents. BMI z-score was standardized by age and gender.

No subjects from Stratum 4 had any measurements for height, weight, and BMI at 1 year and beyond. It is therefore not possible to assess change from baseline for these outcome variables in this stratum.

<u>Height</u>

Median height for all treated subjects at baseline was 140.0 cm (range: 115.6 - 159.0 cm). Changes in height were recorded in 25 subjects from Strata 1 and 2/3 at the 1 year timepoint and in < 25 subjects thereafter. In the CP-CML stratum, there was a weak downward trend over time in height z-score. This was mostly supported by change from baseline in height z-score results, and less so by height percentile shift from baseline tabulation. These results need to be interpreted with caution, since sample sizes were small and decreasing over time. In the Ph+ ALL or AP/BP CML and Ph- ALL/AML stratum there was either insufficient or no data to support qualifying statements about growth in terms of height over time.

Table 7.5.1.1-1: Change from Baseline by Time Period in Height Z-score - All Treated

	CP-CML N = 17	PH+ ALL OR AP/BP-CML N = 17	PH- ALL/AML N = 24	Total N = 58
BASELINE				
N	17	17	22	56
MEAN	-0.114	-0.909	-0.510	-0.511
SD	0.958	1.669	1.454	1.408
MEDIAN	-0.010	-0.760	-0.465	-0.385
Q1, Q3	-0.490, 0.190	-1.850, 0.320	-2.030, 0.450	-1.365, 0.315
MIN, MAX	-2.16, 2.18	-5.29, 1.29	-2.98, 2.14	-5.29, 2.18
CHANGE FROM BASELINE <= 1 YEAR				
N	17	8	0	25
MEAN	-0.128	-0.096		-0.118
SD	0.267	0.231		0.252
MEDIAN	-0.140	-0.155		-0.150
Q1, Q3	-0.320, -0.040	-0.205, -0.030		-0.270, -0.030
MIN, MAX	-0.46, 0.50	-0.39, 0.40		-0.46, 0.50
CHANGE FROM BASELINE > 1 AND <= 2 YEARS				
N	12	4	0	16
MEAN	-0.287	0.105		-0.189
SD	0.419	0.309		0.422
MEDIAN	-0.210	0.050		-0.095
Q1, Q3	-0.620, -0.025	-0.130, 0.340		-0.525, 0.020
MIN, MAX	-0.99, 0.50	-0.19, 0.51		-0.99, 0.51
CHANGE FROM BASELINE > 2 AND <= 3 YEARS				
N	9	3	1	13
MEAN	-0.444	-0.140	-1.340	-0.443
SD	0.640	0.157		0.606
MEDIAN	-0.340	-0.210	-1.340	-0.250
Q1, Q3	-1.070, -0.040	-0.250, 0.040	-1.340, -1.340	-1.070, -0.040
MIN, MAX	-1.27, 0.60	-0.25, 0.04	-1.34, -1.34	-1.34, 0.60
CHANGE FROM BASELINE > 3 AND <= 4 YEARS				
N	8	3	0	11
MEAN	-0.548	-0.257		-0.468
SD	0.439	0.249		0.407
MEDIAN	-0.590	-0.380		-0.420
Q1, Q3	-0.880, -0.195	-0.420, 0.030		-0.750, -0.120
MIN, MAX	-1.15, 0.10	-0.42, 0.03		-1.15, 0.10
CHANGE FROM BASELINE > 4 AND <= 5 YEARS				
N	8	1	0	9
MEAN	-0.416	-0.750		-0.453
SD	0.415			0.404
MEDIAN	-0.360	-0.750		-0.380
Q1, Q3	-0.535, -0.160	-0.750, -0.750		-0.540, -0.340
MIN, MAX	-1.28, 0.06	-0.75, -0.75		-1.28, 0.06
CHANGE FROM BASELINE > 5 YEARS				
N	4	3	0	7
MEAN	-0.305	-0.503		-0.390
SD	0.465	0.350		0.400
MEDIAN	-0.165	-0.490		-0.340
Q1, Q3	-0.645, 0.035	-0.860, -0.160		-0.860, 0.010
MIN, MAX	-0.95, 0.06	-0.86, -0.16		-0.95, 0.06

Note: Patients are only counted once within each time period but can appear in multiple time periods.
Note: If a patient has multiple records within a time period, only the last record within that period is included in the calculation.
Z-Score for height is available for children <= 19 years old (up to age 228 completed months).
Source: Table S.7.1.4

Weight

Median weight for all treated subjects at baseline was 36.55 kg (range: 9.1 - 85.5 kg). Changes in weight were recorded in 53 subjects at the 1 year timepoint; thereafter, fewer than 17 subjects were recorded at each subsequent timepoint. In general, each subject remained in the same percentile weight group, particularly CP-CML subjects. Z-score for weight was calculated only on subjects < 10 years of age (n = 26). Information regarding growth in terms of body weight z-score was too little to support any interpretation for any of the strata.

Table 7.5.1.2-1: Change from Baseline by Time Period in Weight Z-score - All Treated

	CP-CML N = 17	PH+ ALL OR AP/BP-CML N = 17	PH- ALL/AML N = 24	Total N = 58
BASELINE				
N	3	9	14	26
MEAN	0.343	-0.330	0.009	-0.070
SD	1.537	1.033	1.171	1.137
MEDIAN	0.260	-0.370	-0.305	-0.310
Q1, Q3	-1.150, 1.920	-0.910, -0.230	-0.680, 0.560	-0.910, 0.560
MIN, MAX	-1.15, 1.92	-2.04, 1.61	-1.60, 2.51	-2.04, 2.51
CHANGE FROM BASELINE <= 1 YEAR				
N	3	8	12	23
MEAN	0.433	0.314	-0.229	0.046
SD	0.570	0.532	0.478	0.567
MEDIAN	0.350	0.190	-0.205	0.050
Q1, Q3	-0.090, 1.040	-0.065, 0.605	-0.670, 0.180	-0.270, 0.360
MIN, MAX	-0.09, 1.04	-0.27, 1.32	-0.93, 0.44	-0.93, 1.32
CHANGE FROM BASELINE > 1 AND <= 2 YEARS				
N	2	2	0	4
MEAN	0.230	0.180		0.205
SD	0.509	0.184		0.314
MEDIAN	0.230	0.180		0.180
Q1, Q3	-0.130, 0.590	0.050, 0.310		-0.040, 0.450
MIN, MAX	-0.13, 0.59	0.05, 0.31		-0.13, 0.59
CHANGE FROM BASELINE > 2 AND <= 3 YEARS				
N	1	1	0	2
MEAN	0.350	-0.320		0.015
SD				0.474
MEDIAN	0.350	-0.320		0.015
Q1, Q3	0.350, 0.350	-0.320, -0.320		-0.320, 0.350
MIN, MAX	0.35, 0.35	-0.32, -0.32		-0.32, 0.35
CHANGE FROM BASELINE > 3 AND <= 4 YEARS				
N	1	1	0	2
MEAN	0.120	-0.470		-0.175
SD				0.417
MEDIAN	0.120	-0.470		-0.175
Q1, Q3	0.120, 0.120	-0.470, -0.470		-0.470, 0.120
MIN, MAX	0.12, 0.12	-0.47, -0.47		-0.47, 0.12
CHANGE FROM BASELINE > 4 AND <= 5 YEARS				
N	1	1	0	2
MEAN	0.180	-0.670		-0.245
SD				0.601
MEDIAN	0.180	-0.670		-0.245
Q1, Q3	0.180, 0.180	-0.670, -0.670		-0.670, 0.180
MIN, MAX	0.18, 0.18	-0.67, -0.67		-0.67, 0.18
CHANGE FROM BASELINE > 5 YEARS				
N	0	0	0	0
MEAN				
SD				
MEDIAN				
Q1, Q3				
MIN, MAX				

Note: Patients are only counted once within each time period but can appear in multiple time periods.
Note: If a patient has multiple records within a time period, only the last record within that period is included in the calculation.
Z-Score for weight is available for children <= 10 years old (up to age 120 completed months).
Source: Table 8.7.1.5

BMI

At baseline, mean BMI was 18.8 kg/m2 (range: 12.3 to 29.4 kg/m2). Changes in BMI were recorded in 25 subjects from Strata 1 and 2/3 at the 1 year timepoint and in < 25 subjects thereafter. In general, subjects in the low BMI category (underweight) increased their BMI to the healthy range while on study and those with high BMIs remained unchanged or dropped their BMI to a healthier percentile.

In the CP-CML stratum, there was no downward trend over time in BMI z-score. This was based on change from baseline in BMI z-score results and on BMI percentile shift from baseline tabulation. These results need to be interpreted with caution, since sample sizes were small and decreasing over time. In the Ph+ ALL or AP/BP CML and Ph- ALL/AML stratum there was either insufficient or no data to support qualifying statements about growth in terms of BMI over time.

Table 7.5.1.3-1: Change from Baseline by Time Period in BMI Z-score - All Treated Subjects

	CP-CML N = 17	PH+ ALL OR AP/BP-CML N = 17	PH- ALL/AML N = 24	Total N = 58
BASELINE				
N	17	17	22	56
MEAN	-0.015	0.208	0.329	0.188
SD	1.621	1.444	1.092	1.359
MEDIAN	0.310	0.360	0.655	0.455
Q1, Q3	-1.110, 1.040	-0.910, 1.280	-0.770, 1.130	-0.935, 1.150
MIN, MAX	-3.41, 2.57	-2.04, 2.92	-1.27, 2.30	-3.41, 2.92
CHANGE FROM BASELINE <= 1 YEAR				
N	17	8	0	25
MEAN	0.404	0.529		0.444
SD	0.911	0.733		0.844
MEDIAN	0.290	0.750		0.320
Q1, Q3	0.000, 0.630	-0.145, 1.025		0.000, 0.840
MIN, MAX	-1.63, 2.36	-0.51, 1.48		-1.63, 2.36
CHANGE FROM BASELINE > 1 AND <= 2 YEARS				
N	12	4	0	16
MEAN	0.109	-0.253		0.019
SD	0.773	0.572		0.728
MEDIAN	0.115	-0.140		0.055
Q1, Q3	-0.220, 0.645	-0.675, 0.170		-0.300, 0.415
MIN, MAX	-1.67, 1.19	-1.02, 0.29		-1.67, 1.19
CHANGE FROM BASELINE > 2 AND <= 3 YEARS				
N	9	3	1	13
MEAN	0.309	-0.543	1.000	0.165
SD	0.754	0.681		0.809
MEDIAN	0.350	-0.260	1.000	0.350
Q1, Q3	-0.230, 0.780	-1.320, -0.050	1.000, 1.000	-0.260, 0.780
MIN, MAX	-0.96, 1.51	-1.32, -0.05	1.00, 1.00	-1.32, 1.51
CHANGE FROM BASELINE > 3 AND <= 4 YEARS				
N	8	3	0	11
MEAN	0.313	-0.330		0.137
SD	0.805	0.880		0.836
MEDIAN	0.325	-0.310		0.260
Q1, Q3	-0.170, 0.630	-1.220, 0.540		-0.350, 0.540
MIN, MAX	-0.90, 1.83	-1.22, 0.54		-1.22, 1.83
CHANGE FROM BASELINE > 4 AND <= 5 YEARS				
N	8	1	0	9
MEAN	0.313	-0.300		0.244
SD	1.052			1.005
MEDIAN	0.355	-0.300		0.270
Q1, Q3	-0.525, 0.560	-0.300, -0.300		-0.510, 0.450
MIN, MAX	-0.81, 2.53	-0.30, -0.30		-0.81, 2.53
CHANGE FROM BASELINE > 5 YEARS				
N	4	3	0	7
MEAN	1.110	-1.387		0.040
SD	1.417	2.656		2.266
MEDIAN	1.075	-0.660		0.830
Q1, Q3	0.230, 1.990	-4.330, 0.830		-0.660, 1.100
MIN, MAX	-0.59, 2.88	-4.33, 0.83		-4.33, 2.88

Note: Patients are only counted once within each time period but can appear in multiple time periods.
Note: If a patient has multiple records within a time period, only the last record within that period is included in the calculation.
Z-Score for BMI is available for children <= 19 years old (up to age 228 completed months).
Source: Table 8.7.1.6

Bone Age and Pubertal Status (Tanner Stage)

Bone age, a measure of skeletal maturity, was measured by assessment of anteroposterior radiographs of the left hand and wrist obtained on an annual basis. Bone age was measured in 13 subjects (9 subjects from Stratum 1, 4 subjects from Stratum 2/3, 0 subjects from Stratum 4). Tanner stage, an indicator of pubertal status, was measured in 16 subjects (12 subjects from Stratum 1, 4 subjects from Stratum 2/3, 0 subjects from Stratum 4). The values are correlated with what is expected based on the subjects' chronologic age.

Growth Factors

Insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFB-3) subunit are required for maximal growth in children. IGF-1 is produced by many tissues, but the liver is the main source of circulating IGF-1. IGF-1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF-1 is transported by IGFB-3, which also controls its bioavailability and half-life. The secretion patterns of IGF-1 and IGFB-3 mimic each other, their respective syntheses controlled by GH.

Malnutrition is associated with low IGF-1. IGF-1 and IGFB-3 were measured in 15 subjects (11 subjects from Stratum 1, 4 subjects from Stratum 2/3, and 0 subjects from Stratum 4).

IGF-1 and IGFB-3 levels over time were not indicative of any clinical abnormality associated with dasatinib in any strata. However, the limited sample sizes and number of samples in the follow-up period make it difficult to assess the impact of dasatinb on growth factors over time in pediatric subjects.

Hormone Levels

SH levels are measured to test the overall function of the thyroid, a gland that controls metabolism and hormone regulation in the body. Growth and development are commonly affected in children with abnormal thyroid function (hyperthyroidism and hypothyroidism). Normal TSH levels vary depending on age and stage of growth. The normal TSH level for children who have not yet reached puberty is between 0.6 to 5.5 units per milliliter (uU/mL) and for adults and adolescents who have reached puberty is between 0.5 to 4.8 uU/mL.

Free T4 is used to assess thyroid function. High T4 is indicative of hyperthyroidism, while low T4 is indicative of hypothyroidism.

Free T4 was measured in 15 subjects (11 subjects from Stratum 1, 4 subjects from Stratum 2/3, 0 subjects from Stratum 4). TSH was measured in 16 subjects (12 subjects from Stratum 1, 4 subjects from Stratum 2/3, 0 subjects from Stratum 4). All levels were within normal reference ranges for age.

FSH and LH are produced by the pituitary gland and regulate the development, growth, pubertal maturation, and reproductive processes of the body. They are essential for reproduction in both males and females. Normal FSH levels are between 3 and 20 mIU/mL and normal LH levels are between 5 and 20 mIU/mL. FSH and LH levels can fluctuate; however, levels greater than 30 or 40 mIU/mL are indicative of ovarian failure.

One female subject (CP-CML) with a history of unexpected primary ovarian failure and who received chemotherapy before study entry, received study drug from Mar-2007 to Apr-2009, and presented high FSH and LH levels (96-97 U/L and 53-57 U/L) in post treatment. A second female subject (AP-CML) had high FSH and LH levels (118 U/L and 51.8 U/L) during follow up that later normalized with further follow up.

Four other subjects had at least one FSH and LH measurement that was greater than 20 U/L but less than 40 U/L. Due to the limited sample size subjects in the follow up period, and limited number of samples, it is difficult to interpret the impact of dasatinib on hormone levels over time in pediatric subjects.

Long-Term Bone Metabolism Assessments

Urinary N-Telopeptide and Bone Alkaline Phosphatase

Urinary N-telopeptide of type I collagen (NTx) and bone alkaline phosphatase levels over time were monitored as a specific marker of bone resorption.

NTx levels were assessed in 14 subjects (10 subjects from Stratum 1, 4 subjects from Stratum 2/3); min - max in 14 subjects was 18 - 9698 nmol/mmol creatinine. Most subjects had at least one NTx measurement above normal; however, due to the limited sample size subjects in the follow up period, and limited number of samples, it is difficult to interpret the impact of dasatinib on NTx levels over time in pediatric subjects.

Bone alkaline phosphatase levels were assessed in 13 subjects (9 subjects from Stratum 1, 4 subjects from Stratum 2/3); min - max in 13 subjects ranged from 3 - 123 U/L. Generally, bone alkaline

phosphatase results over time were not indicative of any clinical abnormality associated with dasatinib in any strata. However, the assessment of results is difficult due to the limited number of subjects and samples.

Bone Densitometry

In addition to the other growth parameters, dual X-ray absorptiometry (DXA) scan was measured in 12 subjects (8 subjects from Stratum 1, 4 subjects from Stratum 2/3). A bone mineral content or density z-score of more than 2 standard deviations below expected (ie less than -2) should be considered 'low for age'.

No subject in the CP-CML group was considered to be "low for age" per the definition. Two subjects in Stratum 2/3 had low bone density z-scores otherwise.

Serum Electrolytes

Serum electrolytes (sodium, potassium, magnesium, chloride, and phosphorus) were assessed periodically through the treatment period and up to 5 years follow-up. Generally, few subjects had Grade 3 or 4 laboratory abnormalities.

2.3.3. Discussion and conclusion on clinical aspects

Study CA180018 evaluated QD dosing in children and adolescents with relapsed or refractory leukemia. Dasatinib showed encouraging efficacy at the recommended phase 2 dose of 60 mg/m2 QD for pediatric subjects with CP-CML (Stratum 1) and 80 mg/m2 for subjects with Ph+ ALL or AP/BP-CML (Stratum 2/3), as reported previously in the Final CA180018 CSR.

Amendments 05, 06, and 07 added mandatory tests to monitor LTGD at yearly intervals while subjects were on dasatinib study therapy and for up to 5 years of follow-up after the last dose. This Addendum provides cumulative LTGD data collected, long-term efficacy (OS) and safety. There was an AE of Grade 3 growth retardation reported in the final CSR as unresolved in a subject from Strata 1 (CP-CML); during this extended follow-up the AE was completely resolved after approximately 4 years. The subject's final height and weight were 180 cm and 71.1 kg, respectively.

Studies with imatinib treatment in pediatric subjects with CML-CP have reported slower growth for height and effects on endocrine function.10,11,12 TKIs appear to impact growth in Ph + ALL more than that reported for subjects with CML; this could be attributed to the younger age at exposure, or it may also reflect receipt of concurrent multi-drug intensive therapy.

<u>Long-term growth and development parameters</u>

Height, weight, and BMI mean z-scores in dasatinib-treated subjects were relatively unchanged at the end of the follow-up period compared to baseline. The laboratory parameters associated with LTGD and long-term bone metabolism also did not appear to be impacted by dasatinib treatment.

Due to the timing of amendments 05, 06, 07, only 8 subjects were continuing treatment and 10 subjects were in the follow-up period. Some subjects only had one assessment timepoint for one or more of the LTGD parameters. All subjects received prior imatinib before study entry and many also received prior chemotherapy and/or transplant before or after study participation. All these are confounding factors that affect the analysis of the potential effect of dasatinib on growth and development. Therefore, interpretations of this limited data set should be made with caution.

Information that is more relevant will be available from the phase 2 CA180226 study that includes a cohort of subjects naïve to imatinib where the effect of dasatinib would be better assessed.

Overall Survival

The median OS did not change from previously reported results. No additional deaths were reported with the extended follow-up period. Median OS was still not reached in Stratum 1 (CP-CML) subjects.

Overall Safety

With the longer follow-up, no new late toxicities were reported. Dasatinib is well-tolerated and safe in pediatric and adolescent subjects with refractory or relapsed leukemia. The safety profile is consistent with what is expected in this patient population.

2.3.4. CHMP conclusion

Dasatinib is approved for the use in Ph+ CP-CML paediatric subjects based on study CA180226 and CA180018. In CA180018, LTGD assessments were added but due to the timing of the amendments, LTGD data is limited and only available on 18 subjects who were receiving treatment or in follow-up at the time the amendments were implemented. The LTGD data was collected in a subset of subjects for up to 5 years post-treatment.

The benefit risk for the use of dasatinib in imatinib-resistant or imatinib-intolerant CP-CML and newly-diagnosed CP-CML paediatric patients remains positive. The safety profile of dasatinib in the paediatric population is still generally consistent with data reported in adult population. It is agreed that the available information from CA180018 study does not indicate clinically relevant growth and development issues associated with dasatinib treatment in paediatric patients; however, it is difficult to draw any definitive conclusions from the limited data set.

The MAH will monitor risks using routine pharmacovigilance and will update the label as indicated.

It is noted that no update to the product information or RMP is requested based on the submitted data. The current RMP v16.1, states that 'Growth and development disorders and bone mineral metabolism disorders in the pediatric population' has been identified as an 'Important Potential Risk'. Information on effects on growth and development in paediatric patients are included in section 4.4 of the SmPC and section 4.8 includes the general description of the safety profile in paediatric patients. No further updates are considered needed.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Sprycel

Active substance: dasatinib

Study title	Study number	Date of completion	Date of submission of final study report
Phase 1 Study of SRC, ABL Tyrosine Kinase Inhibitor Dasatinib (BMS-354825) in Children and Adolescents with Relapsed or Refractory Leukemia	CA180018	05 May 2020	9 June 2020